REMARKS

Claims 99-125 were elected. Applicants have canceled claim 122. Claim 99 has been amended to replace each reference to a particular group of amino acids (e.g., Group 2 amino acid) with the names of the amino acids within the specified group. Support for this amendment is found on page 20, line 41 to page 21, line 9. Claims 102-119 have been amended to replace one-letter amino acid abbreviations with the name of the amino acid. Claim 123 has been amended as suggested by the examiner. Claims 124 and 125 have been amended to correct their dependency. Claims 126-143, which recite specific amino acid changes listed in claim 99, have been added. No new matter has been added.

Claim Objections

The examiner objected to claim 122 as drawn to non-elected subject matter. Claim 122 has been cancelled.

Rejections Under 35 U.S.C §101

The examiner rejected claims 122-124 as drawn to non-statutory subject matter. Claim 122 has been cancelled. Applicants have amended claim 123 to recite a "fungal cell containing a recombinant nucleic acid molecule comprising the nucleic acid molecule of claim 99" (emphasis added). Claim 124 has been amended to depend only from claim 123. In view of the amendments, applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. §112, First paragraph (written description)

The examiner rejected claims 99-119 and 121-125 under 35 U.S.C. §112, first paragraph as allegedly not supported by an adequate written description. Applicants disagree.

The examiner argued that the claims encompass polypeptides having an "infinite number of amino acid changes". First, the claims do not encompass nucleic acid molecules encoding polypeptides having an infinite number of amino acid changes compared to SEQ ID NO:91.

Second, applicants have provided examples of 41 different functional variants of a polypeptide having the amino acid sequence of SEQ ID NO:91 (lovE).

The claims are not drawn to nucleic acid molecules encoding polypeptides containing an infinite number of amino acid changes relative to SEQ ID NO:91 as suggested by the examiner. Rather the claims are drawn to nucleic acid molecules encoding polypeptides that have an amino acid sequence identical to that of SEQ ID NO:91 except for the presence of one or more of the listed amino acid changes. This is clear from the original language of claim 99. For example, original claim 99 specifies "at least one amino acid change selected from the group consisting of" certain specified amino acid changes. However, to further clarify the claims, applicants have amended claim 99 to recite an "isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide comprising an amino acid sequence that is identical to the amino acid sequence of SEQ ID NO:91 except for the presence of at least one amino acid change selected from the group consisting of..."

The examiner also argued that the present claims do not meet the written description requirement because, according to the examiner, the specification does not unambiguously define which amino acids fall into which groups, i.e., the specification does not disclose which amino acids are Group 2 amino acids, etc. The examiner also argues that the specification only defines what the various groups "typically include" and not what the various groups include under "atypical conditions". Claim 99 has been amended to refer to the specific amino acids falling into each of Groups 1-6 as disclosed in the specification at pages 20-21. This portion of the specification clearly and explicitly defines the amino acids within each of Group 1-6, and these definitions have been incorporated into the present claims.

In view of the forgoing, applicants respectfully request that this rejection under 35 U.S.C. §112, first paragraph be withdrawn.

Rejections Under 35 U.S.C. §112, first paragraph (enablement)

The Examiner rejected claims 99-119 and 121-125 as allegedly not enabled. Applicants respectfully traverse this rejection.

The specification enables those of ordinary skill in the art to make and to use the claimed nucleic acid molecules and cells. Those skilled in the art are capable of using site-directed mutagenesis and other methods to create nucleic acid molecules encoding any desired lovE variant. The variants can be tested for lovE activity using any of the several assays described in the specification (see, e.g., pages 36-49). In one assay a gene conferring resistance to G418 is placed under the control of the lovF promoter, a promoter that is activated by functional lovE. Cells containing this construct and expressing a functional lovE variant will be resistant to G418. In a second assay the beta-galactosidase gene is placed under the control of the lovF promoter. Cells containing this construct and a functional lovE variant will produce beta-galactosidase, an enzyme that can be readily assayed. Finally, since expression of functional lovE is required for lovastatin production by *A. terreus*, in a third assay, lovE variants are tested for the ability to promote production of lovastatin in *A. terreus*.

The specification provides numerous examples of polypeptides having one or more of the amino acid changes specified in claim 99. As can be seen from Table 3 of the specification (page 43) applicants isolated 41 functional lovE variants. Nearly all of these functional variants had two or more amino acid changes and one, lovE 40, had 11 amino acid changes. Some of these functional variants included amino acid changes in addition to those specified in claim 99. The table below provides examples of each of the amino acid changes specified in claim 99 along with the number of different polypeptides that were isolated having each amino acid change (in addition to other amino acids changes).

Type of amino acid change listed in claim 99	Example	Specification	Times Isolated
Phenylalanine changed to valine, leucine, isoleucine, or methionine at position 31	Phenylalanine to Leucine at 31	Table 4 (p. 44)	4
Glutamine changed to lysine, arginine or histidine at position 41	Glutamine to Lysine at 41 Glutamine to Arginine at 41	Table 4 (p. 44) Table 4 (p. 44)	2 3

Threonine changed to valine, leucine, isoleucine, or methionine at position 52	Threonine to Isoleucine at 52	Table 4 (p. 44)	1
Threonine changed to aspartic acid, glutamic acid, asparagine or glutamine at position 52	Threonine to Aspartic acid at 52	Table 4 (p. 44)	1
Cysteine changed to lysine, arginine or histidine at position 73	Cysteine to Arginine at 73	Table 4 (p. 44)	6
Proline changed to serine, threonine or cysteine at position 101	Proline to Serine at 101	Table 4 (p. 44)	1
Proline changed to aspartic acid, glutamic acid, asparagine or glutamine at position 101	Proline to Glutamine at 101	Table 4 (p. 44)	1
Valine changed to leucine, isoleucine, or methionine at position 111	Valine to Isoleucine at 111	Table 4 (p. 44)	2
Serine changed to valine, leucine, isoleucine, or methionine at position 133	Serine to Leucine at 133	Table 4 (p. 44)	2
Glutamic acid changed to valine, leucine, isoleucine, or methionine at position 141	Glutamic acid to Valine at 141	Table 4 (p. 44)	1
Glutamic acid changed to lysine, arginine or histidine at position 141	Glutamic acid to Lysine at 141	Table 4 (p. 44)	1
Cysteine changed to phenylalanine, tyrosine or tryptophan at position 153	Cysteine to Tyrosine at 153	Table 4 (p. 44)	1
Cysteine changed to lysine, arginine or histidine at position 153	Cysteine to Arginine at 153	Table 4 (p. 44)	1
Threonine changed to	Threonine to	Table 4 (p. 44)	2

glycine, alanine or proline at position 281	Alanine at 281		
Asparagine changed to valine, leucine, isoleucine, or methionine at position 367	Asparagine to Isoleucine at 367	Table 4 (p. 44)	2
Asparagine changed to phenylalanine, tyrosine or tryptophan at position 367	Asparagine to Tyrosine at 367	Table 4 (p. 44)	1
Proline changed to serine, threonine or cysteine at position 389	Proline to Serine at 389	Table 4 (p. 44)	1
a Proline changed to valine, leucine, isoleucine, or methionine at position 389	Proline to Leucine at 389	Table 4 (p. 44)	1

As the examiner can see, applicants have identified at least one, and sometimes several, functional lovE variants having each of the amino acid changes listed in claim 99. It is important to note that a number of these amino acid changes were observed in combination with a variety of additional amino acid changes. For example, the change of Phenylalanine to Leucine at position 31 was observed four times. In the case of lovE 20 this amino acid change was observed in combination with a change of Threonine to Isoleucine at position 409. In the case of lovE 21 the change of Phenylalanine to Leucine at amino acid 31 was observed in combination with amino acid changes at positions 97, 113, 146, 163, 367 and 458. In the case of lovE 31 the change of Phenylalanine to Leucine at amino acid 31 was observed in combination with amino acid changes at positions 101, 153, 159, 162, 293 and 311. In the case of lovE 34, the change of Phenylalanine to Leucine at amino acid 31 was observed in combination with amino acid changes at positions 52, 101, 108 and 111. The fact that a particular amino acid change can occur in combination with multiple different additional amino acid changes illustrates that these amino acid changes can be observed in a variety of contexts and still result in a functional protein.

The teachings of the specification, including the description of 41 functional lovE variants having up to 11 amino acid changes, combined with the knowledge of those of ordinary skill in the art, fully enables the present claims.

In view of the forgoing, Applicants respectfully request that these rejections under 35 U.S.C. §112, first paragraph be withdrawn.

Rejections Under 35 U.S.C. §102(b)

The examiner rejected claims 99 and 121-125 under 35 U.S.C. §102(b) as anticipated by U.S. Patent No. 5,849,541. According to the examiner, the TPKS protein disclosed in U.S. Patent No. 5,849,541 anticipates the present claims. As discussed above, the present claims are drawn to nucleic acid molecules encoding proteins having at least one of certain specified amino acids changes compared to SEQ ID NO:91. The TPKS protein does not bear the slightest resemblance to SEQ ID NO:91 and does not fall within the present claims. This can been seen from the alignment of TPKS from U.S. Patent No. 5,849,541 (top line) and SEQ ID NO:91 (second line) shown in Appendix A.

In view of the forgoing, applicants respectfully request that the rejections under 35 U.S.C. §102(b) be withdrawn.

Rejections Under 35 U.S.C. §102(e)

The examiner rejected claims 99-101 and 121-125 under 35 U.S.C. §102(e) as anticipated by U.S. Patent No. 6,391,583. According to the examiner, the lovE protein disclosed in U.S. Patent No. 6,391,583 anticipates the present claims. As discussed above, the present claims are drawn to nucleic acid molecules encoding proteins having at least one of certain specified amino acids changes compared to SEQ ID NO:91. An alignment of SEQ ID NO:91 and the lovE protein of U.S. Patent No. 6,391,583 is shown in Appendix B. As can be see from this alignment, the lovE protein of U.S. Patent No. 6,391,583 includes a stretch of more than 30 amino acids beginning at amino acid 228 that is not present in SEQ ID NO:91. Moreover, the

lovE protein of U.S. Patent No. 6,391,583 does not anticipate the present claims because it does not include any of the amino acid alterations specified in the claims.

In view of the forgoing, applicants respectfully request that the rejections under 35 U.S.C. §102(b) be withdrawn.

Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 23 NOVEMBER 2004

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Appendix A
US5849541 TPKS aligned with SEQ ID NO. 91

Section 7

	(445)	445 450 460 470 480 490 500 518
US5849541 tpks	(445)	IEEYMEPEQNQLRVSNNEDCPPMTGVLSLPLVLSAKSQRSLKIMMEEMLQFLQSHPEIHLHDLTWSLLRKRSVL
seq ID 91	(1)	----------
Consensus	(445)	

Section 8

	(519)	519 530 540 550 560 570 580 592
US5849541 tpks	(519)	PFRRAIVGHSHETIRRALEDAIEDGIVSSDFTTEVRGQPSVLGIFTGQGAQWPGMLKNLIEASPYVRNIVRELD
seq ID 91	(1)	----------
Consensus	(519)	

Section 9

	(593)	593 600 610 620 630 640 650 666
US5849541 tpks	(593)	DSLQSLPEKYRPSWTLLDQFMLEGEASNVQYATFSQPLCCAVQIVLVRLLEAARIRFTAVVGHSSGEIACAFAA
seq ID 91	(1)	----------
Consensus	(593)	

Section 10

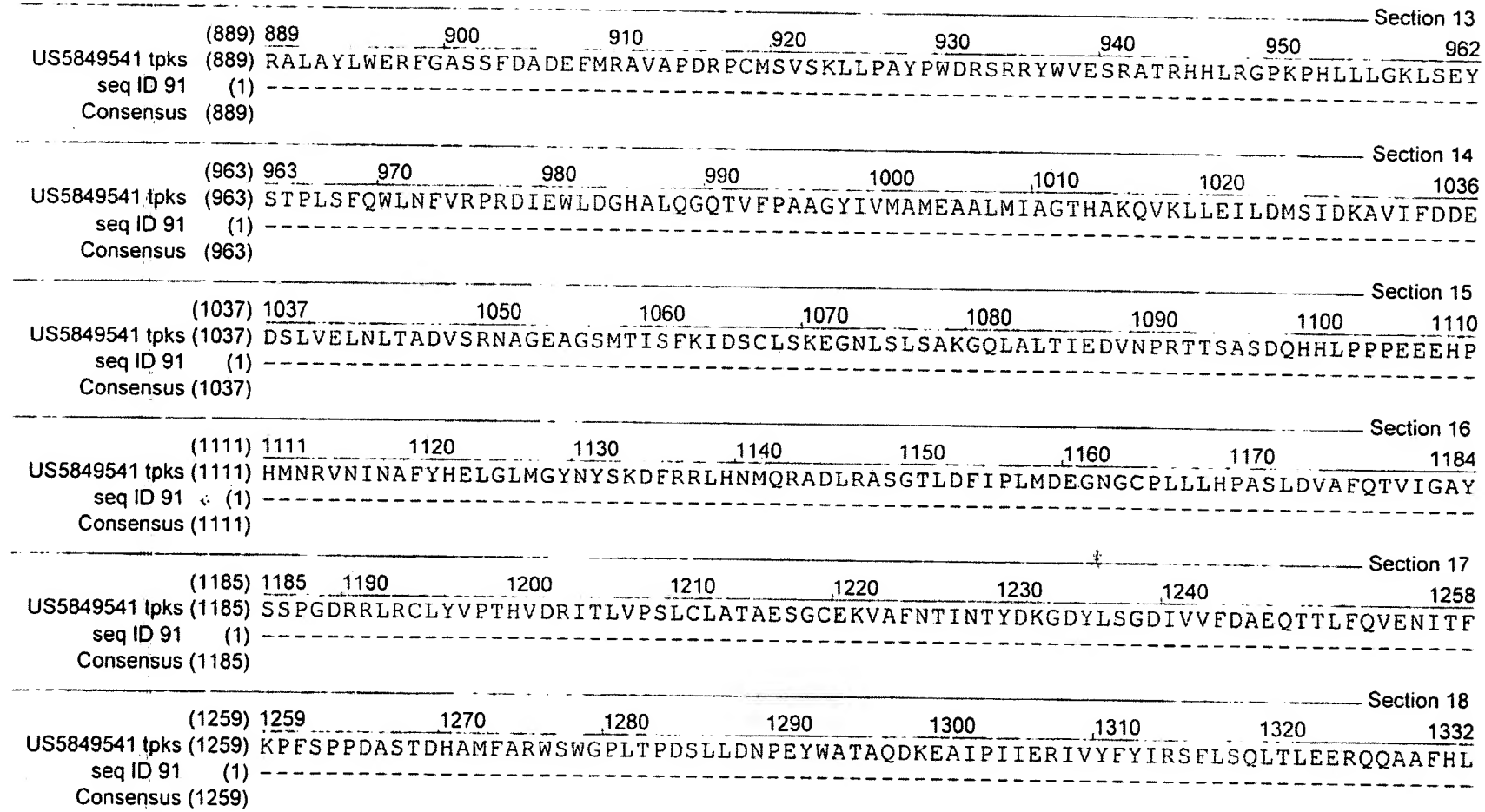
	(667)	667 680 690 700 710 720 730 740
US5849541 tpks	(667)	GLISASLAIRIAYLRGVVSAGGARGTPGAMLAAGMSFEEAQEICELDAFEGRICVAASNSPDSVTFSGDANAID
seq ID 91	(1)	----------
Consensus	(667)	

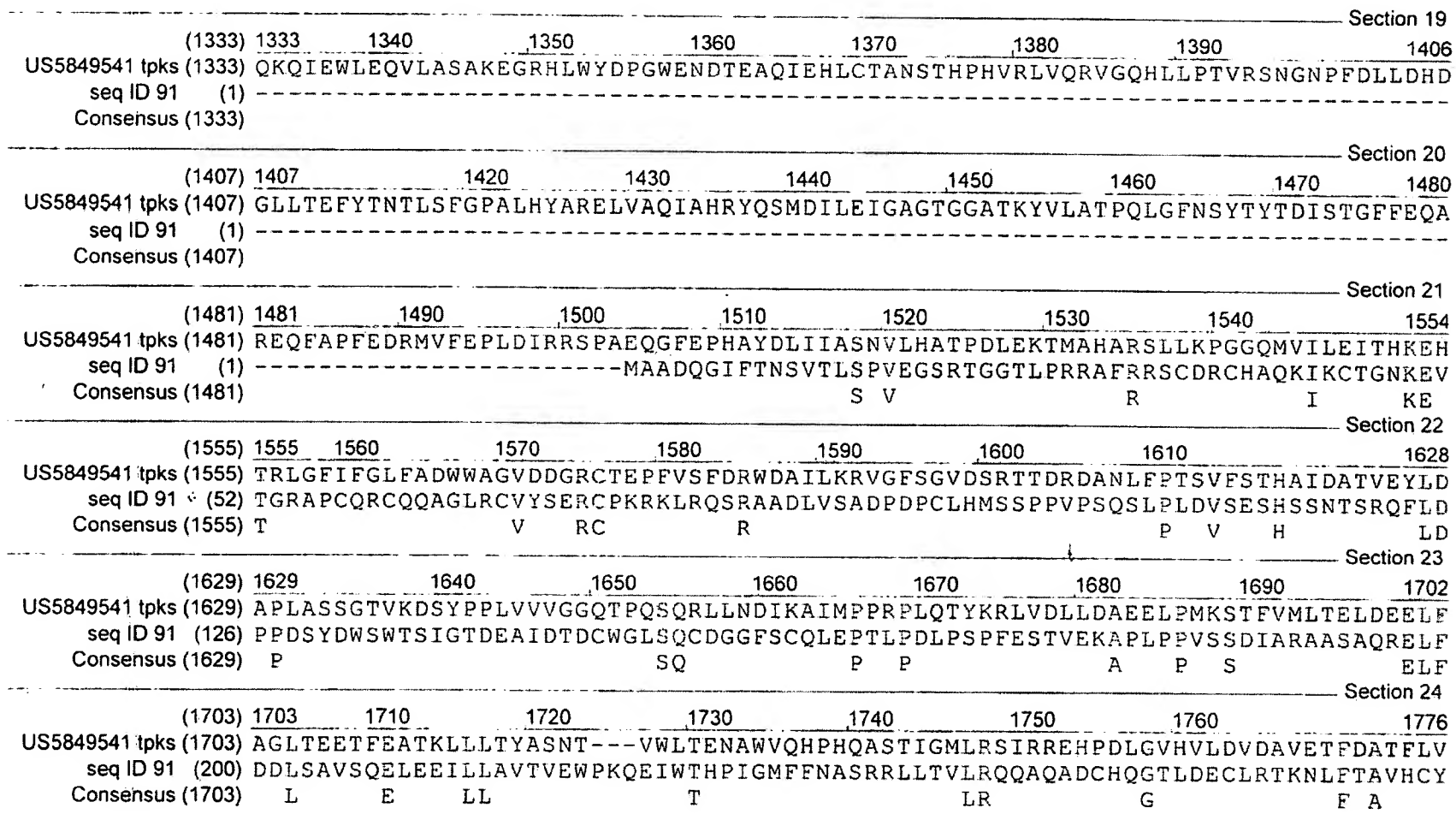
Section 11

	(741)	741 750 760 770 780 790 800 814
US5849541 tpks	(741)	HLKGMLEDESTFARLLKVDTAYHSHHMLPCADPYMQALEECGCAVADAGSPAGSVPWYSSVDAENRQMAARDVT
seq ID 91	(1)	----------
Consensus	(741)	

Section 12

	(815)	815 820 830 840 850 860 870 888
US5849541 tpks	(815)	AKYWKDNLVSPVLFSHAVQRAVVTHKALDIGIEVGCHPALKSPCVATIKDVLSGVDLAYTGCLERGKNDLDSFS
seq ID 91	(1)	----------
Consensus	(815)	


Section 13
(889) 889 900 910 920 930 940 950 962
US5849541 tpks (889) RALAYLWERFGASSFDADEFMRAVAPDRPCMSVSKLLPAYPWDRSRRYWVESRATRHHLRGPKPHLLLGKLSEY
seq ID 91 (1) ----------
Consensus (889)
Section 14
(963) 963 970 980 990 1000 1010 1020 1036
US5849541 tpks (963) STPLSFQWLNFVRPRDIEWLDGHALQGQTVFPAAGYIVMAMEAALMIAGTHAKQVKLLEILDMSIDKAVIFDDE
seq ID 91 (1) ----------
Consensus (963)
Section 15
(1037) 1037 1050 1060 1070 1080 1090 1100 1110
US5849541 tpks (1037) DSLVELNLTADVSRNAGEAGSMTISFKIDSCLSKEGNLSLSAKGQLALTIEDVNPRTTSASDQHHLPPPEEEHP
seq ID 91 (1) ----------
Consensus (1037)
Section 16
(1111) 1111 1120 1130 1140 1150 1160 1170 1184
US5849541 tpks (1111) HMNRVNINAFYHELGLMGYNYSKDFRRLHNMQRADLRASGTLDFIPLMDEGNGCPLLLHPASLDVAFQTVIGAY
seq ID 91 (1) ----------
Consensus (1111)
Section 17
(1185) 1185 1190 1200 1210 1220 1230 1240 1258
US5849541 tpks (1185) SSPGDRRLRCLYVPTHVDRITLVPSLCLATAESGCEKVAFNTINTYDKGDYLSGDIVVFDAEQTTLFQVENITF
seq ID 91 (1) ----------
Consensus (1185)
Section 18
(1259) 1259 1270 1280 1290 1300 1310 1320 1332
US5849541 tpks (1259) KPFSPPDASTDHAMFARWSWGPLTPDSLLDNPEYWATAQDKEAIPIIERIVYFYIRSFLSQLTLEERQQAAFHL
seq ID 91 (1) ----------
Consensus (1259)


Section 19
(1333) 1333 1340 1350 1360 1370 1380 1390 1406
US5849541 tpks (1333) QKQIEWLEQVLASAKEGRHLWYDPGWENDTEAQIEHLCTANSTHPHVRLVQRVGQHLLPTVRSNGNPFDLLDHD
seq ID 91 (1) ----------
Consensus (1333)
Section 20
(1407) 1407 1420 1430 1440 1450 1460 1470 1480
US5849541 tpks (1407) GLLTEFYTNTLSFGPALHYARELVAQIAHRYQSMDILEIGAGTGGATKYVLATPQLGFNSYTYTDISTGFFEQA
seq ID 91 (1) ----------
Consensus (1407)
Section 21
(1481) 1481 1490 1500 1510 1520 1530 1540 1554
US5849541 tpks (1481) REQFAPFEDRMVFEPLDIRRSPAEQGFEPHAYDLIIASNVLHATPDLEKTMAHARSLLKPGGQMVILEITHKEH
seq ID 91 (1) ----------MAADQGIFTNSVTLSPVEGSRTGGTLPRRAFRRSCDRCHAQKIKCTGNKEV
Consensus (1481) S V R I KE
Section 22
(1555) 1555 1560 1570 1580 1590 1600 1610 1628
US5849541 tpks (1555) TRLGFIFGLFADWWAGVDDGRCTEPFVSFDRWDAILKRVGFSGVDSRTTDRDANLFPTSVFSTHAIDATVEYLD
seq ID 91 (52) TGRAPCQRCQQAGLRCVYSERCPKRKLRQSRAADLVSADPDPCLHMSSPPVPSQSLPLDVSESHSSNTSRQFLD
Consensus (1555) T V RC R P V H LD
Section 23
(1629) 1629 1640 1650 1660 1670 1680 1690 1702
US5849541 tpks (1629) APLASSGTVKDSYPPLVVVGGQTPQSQRLLNDIKAIMPPRPLQTYKRLVDLLDAEELPMKSTFVMLTELDEELF
seq ID 91 (126) PPDSYDWSWTSIGTDEAIDTDCWGLSQCDGGFSCQLEPTLPDLPSPFESTVEKAPLPPVSSDIARAASAQRELF
Consensus (1629) P SQ P P A P S ELF
Section 24
(1703) 1703 1710 1720 1730 1740 1750 1760 1776
US5849541 tpks (1703) AGLTEETFEATKLLLTYASNT---VWLTENAWVQHPHQASTIGMLRSIRREHPDLGVHVLDVDAVETFDATFLV
seq ID 91 (200) DDLSAVSQELEEILLAVTVEWPKQEIWTHPIGMFFNASRRLLTVLRQQAQADCHQGTLDECLRTKNLFTAVHCY
Consensus (1703) L E LL T LR G F A

Section 25

```
(1777) 1777                1790        1800        1810        1820        1830        1840        1850
US5849541 tpks (1774) EQVLRLEEHTDELASSTTWTQEPEVSWCKGRPWIPRLKRDLARNNRMNSSRRPIYEMIDSSRAPVALQTARDSS
seq ID 91  (274) ILNVRILTAISELLLSQIRRTQNSHMSPLEGSRSQSPSRDDTSSSSGHSSVDTIPFFSENLPIGELFSYVDPLT
Consensus (1777)      R       EL  S                                RD        SS   I
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Section 26

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(1851) 1851        1860        1870        1880        1890        1900        1910        1924
US5849541 tpks (1848) SYFLESAETWFVPESVQQMETKTIYVHFSCPHALRVGQLGFFYLVQGHVQEGNREVPVVALAERNASIVHVRPD
seq ID 91  (348) HALFSACTTLHVGVQLLRENEITLGVHSAQGIAASISMSGEPGEDIARTGATN---SARCEEQPTTPAARVLFM
Consensus (1851)          T  V           T  VH      A       G              N                V
```

Section 27

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(1925) 1925  1930        1940        1950        1960        1970        1980        1998
US5849541 tpks (1922) YIYTEADNNLSEGGGSLMVTVLAAAVLAETVISTAKCLGVTDSILVLNPPSICGQMLLHAGEEIGLQVHLATTS
seq ID 91  (419) FLSDEGAFQEAKSAGSRGRTIAALRRCYEDIFSLARKHKHGMLRDLNNIPP----------------------
Consensus (1925)      E          GS   T  A      E   S A              N P
```

Section 28

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(1999) 1999        2010        2020        2030        2040        2050        2060        2072
US5849541 tpks (1996) GNRSSVSAGDAKSWLTLHARDTDWHLRRVLPRGVQALVDLSADQSCEGLTQRMMKVLMPGCAHYRAADLFTDTV
seq ID 91  (470) ----------------------------------------------------------------------------
Consensus (1999)
```

Section 29

```
(2073) 2073      2080        2090        2100        2110        2120        2130        2146
US5849541 tpks (2070) STELHSGSRHQASLPAAYWEHVVSLARQGLPSVSEGWEVMPCTQFAAHADKTRPDLSTVISWPRESDEATLPTR
seq ID 91  (470) ----------------------------------------------------------------------------
Consensus (2073)
```

Section 30

```
(2147) 2147        2160        2170        2180        2190        2200        2210        2220
US5849541 tpks (2144) VRSIDAETLFAADKTYLLVGLTGDLGRSLGRWMVQHGACHIVLTSRNPQVNPKWLAHVEELGGRVTVLSMDVTS
seq ID 91  (470) ----------------------------------------------------------------------------
Consensus (2147)
```

Section 31

(2221) 2221 2230 2240 2250 2260 2270 2280 2294
US5849541 tpks (2218) QNSVEAGLAKLKDLHLPPVGGIAFGPLVLQDVMLNNMELPMMEMVLNPKVEGVRILHEKFSDPTSSNPLDFFVM
seq ID 91 (470) ----------
Consensus (2221)

Section 32

(2295) 2295 2300 2310 2320 2330 2340 2350 2368
US5849541 tpks (2292) FSSIVAVMGNPGQANYSAANCYLQALAQQRVASGLAASTIDIGAVYGVGFVTRAELEEDFNAIRFMFDSVEEHE
seq ID 91 (470) ----------
Consensus (2295)

Section 33

(2369) 2369 2380 2390 2400 2410 2420 2430 2442
US5849541 tpks (2366) LHTLFAEAVVAGRRAVHQQEQQRKFATVLDMADLELTTGIPPLDPALKDRITFFDDPRIGNLKIPEYRGAKAGE
seq ID 91 (470) ----------
Consensus (2369)

Section 34

(2443) 2443 2450 2460 2470 2480 2490 2500 2516
US5849541 tpks (2440) GAAGSKGSVKEQLLQATNLDQVRQIVIDGLSAKLQVTLQIPDGESVHPTIPLIDQGVDSLGAVTVGTWFSKQLY
seq ID 91 (470) ----------
Consensus (2443)

Section 35

(2517) 2517 2530 2540 2550 2560 2570 2580 2590
US5849541 tpks (2514) LDLPLLKVLGGASITDLANEAAARLPPSSIPLVAATDGGAESTDNTSENEVSGREDTDLSAAATITEPSSADED
seq ID 91 (470) ----------
Consensus (2517)

Section 36

(2591) 2591 2600 2610 2620 2630 2640 2650 2664
US5849541 tpks (2588) DTEPGDEDVPRSHHPLSLGQEYSWRIQQGAEDPTVFNNTIGMFMKGSIDLKRLYKALRAVLRRHEIFRTGFANV
seq ID 91 (470) ----------
Consensus (2591)

Section 37

(2665) 2665 2670 2680 2690 2700 2710 2720 2738
US5849541 tpks (2662) DENGMAQLVFGQTKNKVQTIQVSDRAGAEEGYRQLVQTRYNPAAGDTLRLVDFFWGQDDHLLVVAYHRLVGDGS
seq ID 91 (470) ----------
Consensus (2665)

Section 38

(2739) 2739 2750 2760 2770 2780 2790 2800 2812
US5849541 tpks (2736) TTENIFVEAGQLYDGTSLSPHVPQFADLAARQRAMLEDGRMEEDLAYWKKMHYRPSSIPVLPLMRPLVGNSSRS
seq ID 91 (470) ----------
Consensus (2739)

Section 39

(2813) 2813 2820 2830 2840 2850 2860 2870 2886
US5849541 tpks (2810) DTPNFQHCGPWQQHEAVARLDPMVAFRIKERSRKHKATPMQFYLAAYQVLLARLTDSTDLTVGLADTNRATVDE
seq ID 91 (470) ----------
Consensus (2813)

Section 40

(2887) 2887 2900 2910 2920 2930 2940 2950 2960
US5849541 tpks (2884) MAAMGFFANLLPLRFRDFRPHITFGEHLIATRDLVREALQHARVPYGVLLDQLGLEVPVPTSNQPAPLFQAVFD
seq ID 91 (470) ----------
Consensus (2887)

Section 41

(2961) 2961 2970 2980 2990 3000 3010 3020 3034
US5849541 tpks (2958) YKQGQAESGTIGGAKITEVIATRERTPYDVVLEMSDDPTKDPLLTAKLQSSRYEAHHPQAFLESYMSLLSMFSM
seq ID 91 (470) ----------
Consensus (2961)

Section 42

(3035) 3035 3041
US5849541 tpks (3032) NPALKLA
seq ID 91 (470) -------
Consensus (3035)

Appendix B
US6391583 lovE aligned with SEQ ID NO. 91

```
(451) 451        460        470        480        490        503
US6391583 lovE (451) FMFLSDEGAFQEAKSAGSRGRTIAALRRCYEDIFSLARKHKHGMLRDLNNIPP
seq ID 91 (417) FMFLSDEGAFQEAKSAGSRGRTIAALRRCYEDIFSLARKHKHGMLRDLNNIPP
Consensus (451) FMFLSDEGAFQEAKSAGSRGRTIAALRRCYEDIFSLARKHKHGMLRDLNNIPP
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